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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

07-JUN-2001

SUBJECT: **Imazapic.** Results of the Health Effects Division (HED) Metabolism Assessment Review Committee (MARC) Meeting Held on 22-MAY-2001. Chemical#s 128943 & 129041. Barcode D275136. Case 291904. Submission S581930.

FROM: William H. Donovan, Ph.D., Chemist *William H. Donovan*
William G. Dykstra, Ph.D., Toxicologist *William Dykstra*
Registration Action Branch 1 (RAB1), HED (7509C)

THROUGH: G. Jeffrey Herndon, Branch Senior Scientist *G. Jeffrey Herndon*
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Christine Olinger, MARC Chair *Christine Olinger*
HED (7509C)

TO: Yan W. Donovan, MARC Executive Secretary
HED (7509C)

1. Attendance

MARC Members at 05/22/2001 Meeting: N. Birchfield, L. Cheng, J. Doherty, Y. Donovan, A. Khasawinah, R. Loranger, and S. Piper.

MARC Members in Absentia: K. Farwell, C. Olinger, A. Protzel, and W. Wassell.

Other Scientists: J. Wolf (EFED), W. Donovan, and W. Dykstra

2. Summary of Deliberations

The metabolism of imazapic in grass, livestock, rotational crops, and water was presented to the HED MARC on 22-MAY-2001 (D274115, W. Donovan and W. Dykstra, 15-MAY-2001).

GRASS

The submitted grass metabolism study showed significant levels of imazapic, CL 263284, and CL 189215 (see Attachment 1), depending on the time interval between herbicide application and sample collection. In the zero-day forage samples, imazapic constituted nearly 90% of the total

radioactive residue (TRR). However, in the forage samples collected 15, 32 and 49 days following treatment, metabolite CL 263284 was the predominate residue. In the hay sample collected 68 days after treatment (DAT), metabolites CL 263284 and CL 189215 were present at similar levels (0.08 ppm).

WATER

Except for rapid aqueous photolysis, imazapic appears to be extremely persistent, mobile and highly soluble. The Committee discussed the degradates identified in the photolysis study and determined that none of these compounds are likely to be more toxic than parent imazapic. Most of them are expected to be less toxic in comparison to the parent. In addition, none of these compounds are expected to occur at significant levels in drinking water as a result of the proposed use. Due to the long half-life of imazapic (aerobic soil $T_{1/2}$ = 2010 days, anaerobic aquatic $T_{1/2}$ = 2400 days), there was some concern that repeated yearly applications could result in a build up of imazapic residues. However, the reference dose (RfD) for imazapic utilizes the most sensitive species and endpoint (1-year dog) and incorporates an uncertainty factor of 300. Nevertheless, all of the current and proposed uses of imazapic occupy a maximum of <1% of the RfD.

ROTATIONAL CROPS

In the submitted rotational crop study, winter wheat was planted 181 DAT, spring wheat and carrots were planted 318 DAT, and lettuce was planted 363 DAT. The TRRs were below 0.01 ppm in all crop matrices studied. However, the petitioner subjected samples with TRRs > 0.003 ppm to characterization/identification procedures and was able to determine that the metabolic pathway in rotational crops is similar to that observed in grass.

LIVESTOCK COMMODITIES

In the submitted goat metabolism and bovine feeding studies, only parent imazapic was fed and identified. The Committee noted that because compounds CL 263284 and CL 189215 are grass metabolites, these compounds may also be consumed by ruminants. Thus, a more realistic feeding study would involve feeding CL 263284. However, as imazapic displays little propensity to accumulate in livestock tissues and the greater polarity of CL 189215 makes it even less likely to accumulate, the Committee did not request a new feeding study using CL 189215 as the dose material at this time.

3. MARC Decisions & Rationale

Grass:

The MARC concluded that for the tolerance expression and risk assessment purposes, the residues of concern in/on grass forage and hay are imazapic, and its metabolites CL 263284 and CL 189215. This decision was based on the toxicological similarity of these three compounds and the significant levels of each found in the grass field trial studies. Although the plant metabolites were not observed in the rat metabolism study, it was

concluded that additional toxicological data on these residues are not necessary.

Drinking Water:

The MARC concluded that for risk assessment purposes, the residue of concern in drinking water is imazapic *per se*. Any photolysis products are expected to be no more toxic than the parent compound and are expected to occur in low levels; thus inclusion of parent only in the drinking water risk assessment should adequately account for risks posed by this chemical.

Rotational Crops:

The MARC concluded that for the tolerance expression and risk assessment purposes, the residues of concern in/on rotational crops are imazapic, and its metabolites CL 263284 and CL 189215. This decision was based on the similarity between the metabolic pathway observed in grass and in rotational crops.

Livestock Commodities:

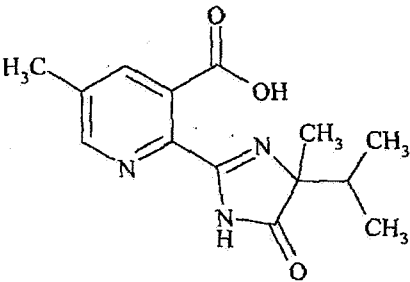
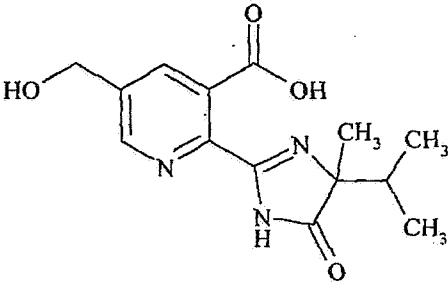
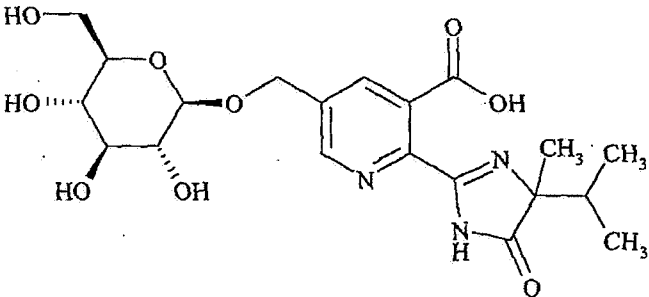
The MARC concluded that for the tolerance expression and risk assessment purposes, the residues of concern in/on livestock commodities are imazapic and its metabolite CL 263284. The decision to regulate metabolite CL 263284 was based on its prevalence in grass forage and hay.

cc (with Attachment 1): W. Donovan, W. Dykstra, O. Odiott, J. Wolf (EFED), J. Tompkins (RD), F. Griffith (BEAD-7503C)

RDI: J. Herndon (07-JUN-2001), RAB1 Chemists (31-MAY-2001), HED MARC (07-JUN-2001)

W. Donovan:CM#2:RM806R:703-305-7330

Attachment 1. Structures of imazapic and its metabolites included in the tolerance expression for peanuts.

 <p>Imazapic; 2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1H-imidazol-2-yl]-5-methyl-3-pyridinecarboxylic acid</p>	 <p>CL 263284 (5-hydroxymethyl derivative); 2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1H-imidazol-2-yl]-5-hydroxymethyl-3-pyridinecarboxylic acid</p>
 <p>CL 189215 (glucose conjugate of CL 263284); nicotinic acid, 5-[β-glucopyranosyloxy)methyl]-2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl</p>	